Conventional diagnostic evaluation (endoscopy, ultrasonography, 24h ambulatory pH monitoring) does not reveal a structural or biochemical abnormality to explain NUD. Attempts at elucidating the pathophysiology of the condition have produced inconsistent findings (6) and a wide array of theories are currently put forward (7).

Serotonin (5HT) is a neurotransmitter both in the enteric nervous system (8) and in the brain (9). It plays a key role in regulating gut physiology, including peristalsis and intestinal tone (10). Animal studies have shown that intracerebroventricular injection of fenfluramine (a serotonin releasing agent) inhibits gastric emptying (11). Selective serotonin reuptake inhibitors, such as fluoxetine and sertraline, are widely used in the treatment of depression and produce a transient syndrome similar to NUD in up to 30% of patients treated (12).

Studies indicate that a central 5HT1a receptor hypersensitivity may be involved in the pathophysiology of NUD (13,14). The release of prolactin from the anterior pituitary is under dopamine inhibition and under 5HT stimulation, probably at the level of the hypothalamus (15). Buspirone is an azaspirodecanedione, which acts as a partial agonist at the 5HT1a receptor (16) and stimulates prolactin release. We have established that prolactin release following buspirone challenge is enhanced in NUD indicating 5HT1a receptor supersensitivity in this condition.

We have demonstrated this in a clinical study that extends our previous findings reported in U.S. Patent No. 5,403,848.

A total of 109 subjects, 50 NUD patients (39 female/11 male) and 59 healthy comparison subjects (32 female/28 male) gave fully informed consent to take part in the study, which had Ethics Committee approval. The mean±SD age of the patients was 35.6±12.2 years (Range 20-62) and of the comparison group 27.2±7.6 years (Range 20-52). At 0830h subjects had a cannula inserted in a forearm vein. Buspirone (30mg) or matching placebo was administered orally at 0900h (Time 0). Blood was taken at 0, 30, 60, 90, 120 and 180min. Prolactin levels rose in all subjects challenged with buspirone. The mean±SD AUC in patients was 46±35 and in healthy subjects 24±35. A 2-way repeated measures ANOVA yields a significant group X time interaction with differences significant at 60min ($p<0.05$), 90 min ($p<0.01$) and 120 min ($p<0.05$). Prolactin concentration at 90 min provided the best discrimination between the two groups.

According to the present invention, what is required to treat non-ulcerative dyspepsia is the administration of effective amounts of a substance that reduces the sensitivity of 5HT1a receptors and we have discovered that pindolol, which has affinity for 5HT1a receptors has beneficial effects in subjects suffering from non-ulcerative dyspepsia.

SUMMARY OF THE INVENTION

The present invention provides a means for prevention and treatment of gastrointestinal disease by administration of a substance that reduces the sensitivity of 5HT1a receptors. A preferred means is the administration of RS pindolol or a salt thereof. An especially preferred means is the administration of S (-) pindolol or a salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

As noted earlier, this invention can use any substance that is an antagonist or a partial agonist of 5HT1a receptors such that the sensitivity of 5HT1a receptors described above is reduced.

Pindolol is a beta adrenergic antagonist, used in the treatment of hypertension and angina. It also has affinity for 5HT1a receptors of a similar magnitude as its affinity for beta adrenergic receptors. Until now, no therapeutic applications of this phenomenon have been discovered. Pindolol is used therapeutically in hypertension and angina as the racemic substance, RS pindolol. Most or all of the pharmacological effects of pindolol are possessed by the isomer S (-) pindolol. The present invention utilizes pindofol to reduce the sensitivity of 5HT1a receptors and as a result to provide the means for prevention and treatment certain gastrointestinal diseases, including non-ulcerative dyspepsia. A preferred embodiment of the invention is the isomer S (-) pindolol or salts thereof. Another method utilizes the administration of cyproheptadine, described in U.S. Patents 5,324,738 and 5,403,848. The latter also describes a method for diagnosis of non-ulcerative dyspepsia by measuring the

responsiveness of 5HT1a receptors. RS pindolol has an advantage over cyproheptadine of greater selectivity for the 5HT1a receptor and S (-) pindolol has further advantages of greater potency and specificity.

The invention is likely to be effective in various presentations of gastrointestinal disease in which there is altered sensitivity of 5HT1a receptors. We have specific demonstration of the role of 5HT1a receptors in non-ulcerative dyspepsia, but there is likely to be also benefit in certain cases of irritable bowel syndrome, especially that occurring in the upper intestinal region and in certain cases of motility disorders (including nausea) caused by cancer chemotherapy.

Various pharmaceutical presentations are possible, including (but not limited to) tablets, capsules, oral solutions and suspensions and parenteral solutions. Included are also pharmaceutical formulations for oral use in which the active substance is released in a controlled and slower fashion such that the treatment may be administered less frequently.

The usual doses of RS pindolol and S (-) pindolol will be in the range of 2.5mg to 50mg daily in single or divided doses, depending upon the therapeutic response and the pharmaceutical form. The usual doses of S (-) pindolol will be lesser than those of RS pindolol since the former will be more potent because it is responsible for most or all of the pharmacological effects.

The invention is intended for the treatment of mammals, including humans.

The ability of the invention to treat gastrointestinal disease has been demonstrated in a clinical study.

EXAMPLE

Eleven patients suffering from non-ulcerative dyspepsia were recruited to a clinical study and gave informed consent. All were treated with pindolol 2.5mg three times daily. Seven of the 11 patients showed a significant improvement in symptoms within 1 week of commencing treatment. A further patient improved in the second week. Their responses were quantified using a standard rating scale (GSRS scores). The results demonstrated a substantial improvement with a reduction in average symptom severity of approximately 68% in three weeks, with the greatest improvement observed within one week.

Table 1. Mean symptom score (average of 11 patients)

Week	Mean GSRS Score
0	9
1	4.2
2	3.5
3	2.9

REFERENCES TO PREVIOUS PATENTS

T.G. Dinan and P.W.N. Keeling U.S. Patent No. 5,324,783
T.G. Dinan and P.W.N. Keeling U.S. Patent No. 5,403,848

OTHER REFERENCES

1. Fisher RS, Parkman HP. Management of nonulcer dyspepsia. N Engl J Med 1998;339:1376-81.
2. Brown C, Rees EWE. Dyspepsia in general practice. BMJ 1990;300:829-30.
3. Nyren O, Adami HO, Gustavsson S, Loof L. Excess sick-listing in nonulcer dyspepsia. J Clin Gastroenterol 1986;8:339-45.
4. Talley NJ, Colin-Jones D, Koch KI, Koch M, Nyren O, Stranghellini V. Functional dyspepsia: a classification with guidelines of diagnosis and management. Gastroenterol Int 1991;4:145-60.
5. Talley NJ, Zinsmeister AR, Schleck CD, Melton LJ. Dyspepsia and dyspepsia subgroupings: a population-based study. Gastroenterology 1992;102:1259-68.
6. Talley NJ, Philips SF. Non-ulcer dyspepsia: potential causes and pathophysiology. Ann Intern Med 1988;108:865-79.
7. Dotevall G. Psychosomatic gastroenterology today and some ideas for tomorrow. Gastroenterol Int 1989;2:96-100.
8. Gershon MD, Erde SM. The nervous system of the gut. Gastroenterology 1981;80;1571-94.
9. Baumagarten HG, Grozdanovic Z. Neuroanatomy and neurophysiology of central serotonergic systems. J Serotonin Res 1994;1:171-81.
10. Lundgren O, Svanvik J, Jivegard L. Enteric nervous system: 1. Physiology and pathophysiology of the intestinal tract. Digest Dis Sci 1989;34:264-83.
11. Rowland N, Carlton J. Inhibition of gastric emptying by peripheral and central fenfluramine in rats: correlation with anorexia. Life Sci 1984;34:2495-9.
12. Thakore JH, Berti C, Dinan TG. Treating depression with specific serotonergic acting agents. J Serotonin Res 1996;3:145-160.
13. Dinan TG, Yatham LN, Barry S, Chua A, Keeling PWN. Serotonin supersensitivity: the pathophysiologic basis of non-ulcer dyspepsia? A preliminary report of buspirone/prolactin responses. Scand J Gastroenterol 1990;25:541-44.

14. Chua A, Keating J, Hamilton D, Keeling PWN, Dinan TG. Central serotonin receptors and delayed gastric emptying in in-ulcer dyspepsia. BMJ 1992;305:280-2.

15. Lamberts SWJ, Macleod RM. Regulation of prolactin secretion at the level of the lactrotroph. Physiol Rev. 1990;70:279-318.

16. Meltzer HY, Maes M. Effects of buspirone on plasma prolactin and cortisol levels in major depressed and normal subjects. Biol Psychiat.1994;35:316-323.